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PATENT

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In the United States Patent and Trademark Office

Applicant: Weickert et al.
Applicant's Ref: 0067.00
Application No: 10/032,239
Filed: December 21, 2001
Title: PULMONARY DELIVERY OF POLYENE ANTIFUNGAL AGENTS

Examiner: Wang, Shengjun
Group Art Unit: 1617

October 6, 2006
San Carlos, California

AMENDED APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Examiner's Final Rejection of July 14, 2004, the Applicant of the above-referenced patent application (hereinafter Appellant) hereby appeals to the Board of Patent Appeals and Interferences. Appellant requests the reversal of the Final Rejection. This Brief is supplemental to, and amends, the Appeal Brief filed 15 August 2005, and the Supplemental Appeal Brief, filed July 7, 2006.

The fee required under § 1.17 has been paid previously. A request and fee for a one month extension are included in the accompanying Transmittal of Appeal Brief.

This Brief contains the following headings, in the order set forth below pursuant to 37 CFR § 41.37(c)(i):

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I *Real Party in Interest*

The real party in interest of the present application is Nektar Therapeutics, Inc. (formerly Inhale Therapeutic Systems, Inc.), having a place of business at 150 Industrial Road; San Carlos, California 94707. Nektar Therapeutics, Inc. is owner by assignment.

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II *Related Appeals and Interferences*

Appellant, Appellant's legal representative, and assignee are aware of no appeals, interferences, or related judicial or administrative proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

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III *Status of Claims*

A. Total Number of Claims in the Application

Claims in the application: 1-60

B. Status of All Claims in the Application

Claims Pending: 40-59

Claims Rejected: 40-59

Claims Cancelled: 1-39 and 60

Claims Allowed: None

Claims Withdrawn: None

C. Claims on Appeal

The claims on appeal are: 40-59.

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IV *Status of Amendments*

No amendments after final have been filed. Applicant's amendment filed on April 16, 2004 has been entered.

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V. *Summary of claimed subject matter*

A. Overview

The present invention is directed to an inhaleable, spray dried powder formulation comprising a polyene antifungal agent, such as Amphotericin B. Polyenes possess very low solubilities in water and in conventional organic solvents. Thus, formulation of these compounds outside of dry mixing is extremely difficult. The solubility of the polyene can be increased under extreme conditions of pH. However, such conditions typically lead to significant levels of degradation of drug and are usually considered undesirable for the formation of powders for direct administration to the lung.

The present inventors were faced with the challenge of trying to find conditions for spray drying the highly insoluble drug, such as amphotericin B, that (i) did not promote high levels of degradation of drug, (ii) were economically practical, and (iii) resulted in the formation of aerosolizable particles suitable for inhalation.

The presently described and claimed invention relates to the result of this effort. Described are methods for spray drying polyene antifungal agents that result in the formation of chemically stable yet highly dispersible powders. That is to say, the antifungal powders of the invention have excellent aerosol characteristics, such that they are reproducibly prepared and can be efficiently administered by inhalation to the lung, while exhibiting good chemical and physical stability, thus providing efficacious results.

B. Concise Explanation of Subject Matter of Each Independent Claim

References in bold are to page and line numbers of the specification. The cited page and line numbers are not to be construed as exclusive support for the claimed element(s).

Independent Claim 40

The claim is directed to a dry powder for inhalation, **(page 3, line 23)** the dry powder produced by dissolving **(page 20, lines 3-5)** a polyene antifungal compound **(page 3, line 24)** in an acidified solvent **(page 4, line 14)** to form an acidic polyene-containing solution **(page 4,**

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lines 17-21), and spray drying the polyene-containing solution **(page 4, line 14)** to form an inhaleable dry powder **(page 4, line 15)** containing no more than about 10% polyene degradation products **(page 4, line 15)** and characterized by an emitted dose greater than 60% **(page 4, line 16)**.

Independent Claim 41

The claim is directed to a dry powder **(page 3, line 23)** produced by suspending a polyene antifungal compound **(page 21, lines 6-7)** in an aqueous solvent **(page 21, line 9)** to form a suspension, wet milling the suspension, **(page 21, line 9)** and spray drying the wet milled suspension **(page 21, line 7)** to produce an inhaleable dry powder containing no more than about 10% polyene degradation products **(page 26, line 16)** and characterized by an emitted dose greater than about 60% **(page 25, line 26)**.

Independent Claim 42

The claim is directed to a spray-dried powder composition for oral inhalation **(page 3, line 23)** comprising a therapeutically effective amount of a polyene antifungal compound, **(page 14, lines 5-6)** wherein the composition comprises no more than about 10% polyene degradation products **(page 26, line 16)** and is characterized by an emitted dose greater than about 60% **(page 25, line 26)**.

Dependent claims 43-56 are further directed to the composition for oral inhalation as recited in claim 42.

Independent Claim 57

The claim is directed to a spray-dried powder composition for oral inhalation **(page 3, line 23)** comprising a therapeutically effective amount of a polyene antifungal compound **(page 14, lines 5-6)** and a leucyl-containing excipient **(page 17, lines 8-10)** comprising from 1 to 3 amino acid residues. **(page 8, line 3)**

Independent Claim 58

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The claim is directed to an aerosolized, spray-dried powder composition for oral inhalation **(page 4, lines 7-11)** comprising a therapeutically effective amount of a polyene antifungal compound, **(page 14, lines 5-6)** wherein the composition comprises no more than about 10% polyene degradation products **(page 26, line 16)** and is characterized by an emitted dose greater than about 60% **(page 25, line 26)**.

Dependent claim 59 is further directed to the composition for oral inhalation as recited in claim 58.

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VI *Grounds of Rejection to be Reviewed on Appeal*

Appellant requests review of the Examiner's following grounds of rejection:

(i) Claims 40 and 42-59 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,965,156 to Proffitt et al (hereinafter Proffit et al), in view of PCT Publication WO 97/03649 to Staniforth et al (hereinafter Staniforth et al) and U.S. Patent 6,077,543 to Gordon et al (hereinafter Gordon et al); and

(ii) Claim 41 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Proffitt et al, in view of Staniforth et al, Gordon et al, and further in view of U.S. Patent 4,016,254 to Seager (hereinafter Seager). [Note that it is believed the Examiner intended to reject claim 41 under these grounds, rather than claim 42 as typed in the Final Office Action.]

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VII *Argument*

Appellant believes each of claims 40-59 to be improperly rejected and to therefore be allowable for the at least the following reasons.

The Examiner improperly rejected independent claim 40 under 35 USC 103(a) as being unpatentable over Proffitt et al in view of Staniforth et al and Gordon et al. Claim 40 is to a dry powder for delivery by inhalation to the lungs, the dry powder produced by a method comprising: (i) dissolving a polyene antifungal compound in an acidified solvent to form an acidic polyene-containing solution, and (ii) spray drying said polyene-containing solution to form an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than 60%. As discussed below, Proffitt et al does not disclose or suggest the powder as claimed. In addition, the teachings of Staniforth et al and Gordon et al would not suggest a modification of Proffitt et al that arrives at the presently claimed invention. Thus, the invention of claim 40 would not have been obvious to one having ordinary skill in the art at the time the invention was made.

Proffitt et al does not render claim 40 unpatentable singly or in combination. Claim 40 is directed to a dry powder for delivery by inhalation to the lungs. In contrast, Proffitt et al discloses a liposomal polyene formulation that is dried and then re-hydrated so that it may be delivered intraveneously to treat systemic fungal infections (see column 4 lines 20-54). Thus, Proffitt et al is not a dry powder for delivery by inhalation to the lungs. The fact that the Proffitt et al powder is dried at one time during its processing does not make it "a dry powder for delivery by inhalation to the lungs". For a dry powder to be deliverable to the lungs it can not be a powder that is prone to hydration. Hydration during storage and/or during delivery in a humid environment will change the aerodynamic character of the powder and will limit the effectiveness of the active agent reaching the lungs. A powder such as the powder of Proffitt et al which is specifically designed to re-hydrate and not specifically designed for inhalation delivery would not be suitable for inhalation delivery. Furthermore, claim 40 recites that the emitted dose, i.e. the dose as defined on page 9 of Appellant's specification, is at least 60%. The presumption by the Examiner that the Proffitt et al powder which is not designed for inhalation delivery would have an emitted dose of at least 60% is, at best, speculative.

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In addition, one of ordinary skill in the art would not have found it obvious to modify Proffitt et al in view of Staniforth et al and Gordon et al to change Proffitt et al's formulation to one that is a powder that is delivered to the lungs because doing so would go against the teachings of Proffitt et al. Proffitt et al is concerned with (1) a manner of making an injectable polyene formulation on a large scale and (2) the treatment of systemic fungal infections. Both of these teachings would be destroyed by the Examiner's proposed modification. Accordingly, not only is there no motivation for one of ordinary skill in the art to make the proposed modification to Proffitt et al, but the person of ordinary skill would be taught away from doing so in that it would destroy the entire purpose of the primary reference. For at least these reasons, Applicant requests withdrawal of the rejection of claim 40.

Claim 41 is also not rendered unpatentable by Proffitt et al. Claim 41 is to a dry powder made by a process comprising, inter alia, suspending a polyene antifungal compound in an aqueous solvent to form a suspension and spray drying the suspension. Proffitt et al teaches a polyene solution and does not teach a polyene suspension that is spray dried. The teachings of Staniforth et al, Gordon et al, and Seager et al do not make up for the deficiencies of Proffitt, and one of ordinary skill in the art would not have found it obvious to modify the process of Proffitt et al based on these teachings, particularly in the absence of motivation to do so.

Independent claims 42, 57 and 58 are not rendered unpatentable by the applied references, either. Claims 42, 57 and 58 are to powder compositions suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound. As discussed above, Proffitt et al does not disclose an inhaleable formulation and teaches away from a modification that would result in an inhaleable formulation. Therefore, claims 42, 57, and 58 and claims 43-56 depending from claim 42 are not rendered unpatentable by Proffitt et al, Staniforth et al, and Gordon et al.

Independent claim 57 is not rendered unpatentable by the applied references, for the further reason that neither Proffitt et al, Staniforth et al., nor Gordon et al, singly or in combination teach or suggest a spray-dried powder composition for oral inhalation comprising a therapeutically effective amount of a polyene antifungal compound and a leucyl-containing excipient.

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For at least these reasons, Appellant requests that the rejection of claims 40-59 be overturned and requests an indication of the allowability thereof.

Conclusion

Thus, it is believed that all rejections made by the Examiner have been addressed and overcome by the above arguments. Therefore, all pending claims are allowable. A reversal is respectfully requested.

Should there be any questions, Appellant's representative may be reached at the number listed below.

Respectfully submitted,

NEKTAR THERAPEUTICS

Dated: 10/6/06

By: _____
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VIII CLAIMS APPENDIX

The following claims are involved in the appeal:

40. A dry powder for delivery by inhalation to the lungs, the dry powder produced by a method comprising:

(i) dissolving a polyene antifungal compound in an acidified solvent to form an acidic polyene-containing solution, and

(ii) spray drying said polyene-containing solution to form an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than 60%.

41. A dry powder produced by a method comprising:

(i) suspending a polyene antifungal compound in an aqueous solvent to form a suspension,

(ii) wet milling the suspension from (i) to form a wet-milled suspension, and

(iii) spray drying the wet milled suspension to produce an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than about 60%.

42. A spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound, wherein the composition comprises no more than about 10% polyene degradation products and is characterized by an emitted dose greater than about 60%.

43. The powder composition of claim 42, containing no more than about 5% polyene degradation products.

44. The powder composition of claim 42, wherein the powder comprises particles having an MMAD of less than about 5 microns.

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45. The powder composition of claim 44, wherein the powder comprises particles having an MMAD of less than about 3.5 microns.

46. The powder composition of claim 42, which is non-proteinaceous.

47. The powder composition of claim 42, wherein said polyene is nystatin or amphotericin B.

48. The powder composition of claim 42, wherein said polyene is non-encapsulated.

49. The powder composition of claim 48, wherein said polyene is non-liposome and non-polymer encapsulated.

50. The powder composition of claim 42 substantially comprising neat polyene.

51. The powder composition of claim 42, further comprising a pharmaceutically acceptable excipient.

52. The powder composition of claim 51, wherein said excipient is selected from the group consisting of buffers, leucine, and trileucine.

53. The powder composition of claim 51, comprising at least about 30% by weight polyene.

54. The powder composition of claim 53, comprising at least about 50% by weight polyene.

55. The powder composition of claim 42, having a water content greater than about 4% by weight.

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56. The powder composition of claim 55, having a water content ranging from about greater than 4% by weight to about 10% by weight.

57. A spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound and a leucyl-containing excipient comprising from 1 to 3 amino acid residues.

58. An aerosolized, spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound, wherein the composition comprises no more than about 10% polyene degradation products and is characterized by an emitted dose greater than about 60%.

59. A method for treating or preventing fungal infection in a subject in need thereof, said method comprising administering to said subject by oral inhalation a therapeutically effective amount of a spray dried powder composition of claim 42 in aerosolized form.

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IX EVIDENCE APPENDIX

None

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X RELATED PROCEEDINGS APPENDIX

None

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